PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	Examiner: Robinson, B.
Richard A. MUELLER *et al.*	)	
	)	Group Art Unit: 1625
Serial No.: 09/625,384	)	
	)	Atty Dkt No.: 101765.00054
Filed: July 26, 2000	)	(3128/1)

For: RETROVIRAL PROTEASE INHIBITORS

APPEAL BRIEF

Mail Stop: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.192, Appellants submit this Appeal Brief, in triplicate, to the Board of Appeals and Interferences in support of Appellants' July 14, 2003 Notice of Appeal. Appeal is taken from the Final Office Action dated January 14, 2003. Appellants request a two-month extension of time to file this Appeal Brief, from September 14, 2003 up to and including November 14, 2003. Appellants authorize the Commissioner to charge our Deposit Account No. 19-0733 a total of $750, the sum of the fees for filing this Appeal Brief ($330) and for the two-month extension of time ($420). No additional fees are believed to be due. However, should any additional fees be required or an overpayment of fees made, please credit or debit our Deposit Account No. 19-0733, accordingly.

REAL PARTY IN INTEREST

The owner of this application and the real party in interest is G. D. Searle &

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 1-99 were originally filed and claims 1-18 and 38-99 stand withdrawn as the result of a restriction requirement. Claims 19-37, involved in this appeal, stand finally rejected and are reproduced in the attached Appendix I. The pending and withdrawn claims 1-18 and 38-99 are reproduced in the attached Appendix II.

No claim is allowed.

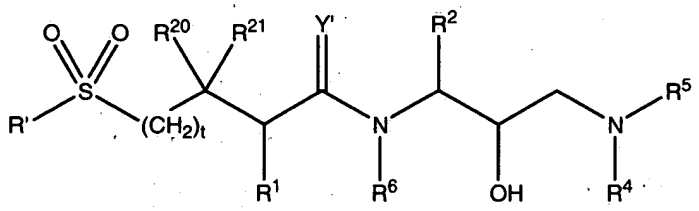
STATUS OF AMENDMENTS

No claim amendments have been filed subsequent to the Final Office Action dated January 14, 2003.

SUMMARY OF THE INVENTION

As defined by claims 19-37 involved in this appeal, the present invention is directed to a class of retroviral protease inhibitor compounds, to pharmaceutical compositions comprising the inhibitor compounds, and to methods of treatment using the inhibitor compounds. The inhibitor compounds are effective in preventing the replication of retroviruses such as human immunodeficiency virus (HIV).

In particular, the invention of independent claim 19 is directed to novel retroviral protease inhibitor compounds of the following Formula II:



or a pharmaceutically acceptable salt, prodrug, or ester thereof, as described on page 7, lines 10-25. The substituents R', t, R^{20}, R^{21}, R^1, Y', R^6, R^2, R^4, and R^5 are defined on page 7, line 27 to page 29, line 1 of the specification. Dependent claim 20 recites a sub-generic group of compounds, wherein R^4 and R^5 together with the nitrogen to which they are bonded represent an N-heterocyclic moiety, as described on page 21, lines 24-28. Dependent claim 21 recites a sub-generic group of N-heterocyclic moieties having formulae as described on page 22, line 1 to page 24, line 1. Dependent claims 22-30 recite other sub-generic groups of compounds, limiting various substituents as defined in independent claim 19. Dependent claims 29 and 30 also limit the stereochemistry of carbon atoms to which the R^2 (limited to phenylthiomethyl in these claims) and the hydroxyl substituents are attached, as described on page 25, lines 4-10.

Claims 31 and 32 recite pharmaceutical compositions comprising a compound of claim 19 and one or more pharmaceutically acceptable carriers, as described on page 164, line 19 to page 167, line 9. Claims 33-35 recite methods of inhibiting a retroviral protease, treating a retroviral infection, and treating an HIV infection, respectively, the methods comprising administering a compound of claim 19 or a pharmaceutical composition comprising a compound of claim 19, as described on page 1, lines 9-18. Claims 36-37 recite methods for treating AIDS comprising administering the

pharmaceutical compositions comprising a compound of claim 19, alone or in combination with other drugs for the treatment of AIDS or the symptoms of AIDS, as described on page 167, line 11 to page 168, line 9.

ISSUES

The issues presented to the Board for review by this appeal are:

(I) Whether claims 34 and 37 are unpatentable under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Appellants regard as their invention.

(II) Whether claims 19-37 are unpatentable under 35 U.S.C. § 112, first paragraph, for lacking enablement for making and using compounds within the claim scope.

(III) Whether the Examiner's proposed *additional* (*i.e.*, not the original) restriction requirements set forth a restriction group that encompasses Appellants' elected species.

(IV) Whether, after electing a species according to a first restriction requirement, Appellants are then entitled to examination on the merits of claims 19-37, reading on the elected species, and are not instead required to further restrict these claims to specified Markush members.

GROUPING OF CLAIMS

The rejected claims stand or fall together.

ARGUMENT

I. CLAIMS 34 AND 37 ARE DEFINITE UNDER 35 U.S.C. § 112, SECOND PARAGRAPH.

Claims 34 and 37 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that Appellants regard as their invention. The Final Office Action contends that the phrases "a retroviral infection" (claim 34) and "in combination with other drugs" (claim 37) are indefinite because no particular retroviral infection or other drug is being claimed. Appellants respectfully appeal the final rejection of these claims.

Regarding claim 34, retroviral infections are well known and have a definite meaning to the ordinary skilled artisan. In particular, retroviral infections arise from HIV and other lentiviruses such as HIV-2, respiratory syncitial virus, hepadnavirus, picornavirus, and cytomegalovirus. Not only are retroviral infections well known, the above retroviruses and others are disclosed in U.S. Patent No. 5,756,533, incorporated into the application by reference. The '533 patent also discloses the treatment of retroviral infections by inhibiting retroviral protease.

If the claims, read in light of the specification, reasonably apprise those skilled in the art of the scope of the invention, the definiteness requirement of § 112 is met. *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Because the meaning of "a retroviral infection" is well known in the art and is also clear from the specification, Appellants submit that claim 34 is not made indefinite simply because no *specific* retrovirus, or disease (*e.g.*, AIDS) resulting from a retroviral infection, is recited.

The Final Office Action's contention that Appellants have "not shown how all of these various retroviral infections or even most of them can be treated" by the claimed compounds has absolutely no bearing on the issue of whether the claim is definite within the meaning of 35 U.S.C. § 112, second paragraph, in view of the use of the phrase "a retroviral infection" therein.

Regarding claim 37, the phrase in question is not simply "in combination with other drugs." Rather, the phrase is "in combination with other drugs for the treatment of AIDS or the symptoms of AIDS." Appellants respectfully submit that the meaning of "drugs for the treatment of AIDS or the symptoms of AIDS" is not only known in the art but is also set forth in the specification at page 167, line 10 to page 168, line 10. In contrast to what the Office Action contends, the claim is not rendered indefinite merely because it encompasses "a vast array of drugs with varying structures." It is well established that breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 U.S.P.Q. 597 (C.C.P.A. 1971) and MPEP § 2173.04.

During a personal interview on July 3, 2003, the Examiner suggested to Appellants' undersigned representatives that the rejection would stand simply because the chemical formulas of these other drugs were not disclosed and claimed. Appellants respectfully submit, however, that it is unnecessary to specifically identify the chemical formulas of these drugs. A patent specification is not required to be as detailed as a production blueprint. Some experimentation and exercise of judgment is to be expected in adapting an invention to a particular use. *Douglas v. U.S.*, 510 F.2d 364, 366 (Ct. Cl. 1975). In this case, the invention of claim 37 is directed to the particular use of combination therapy with the claimed compounds.

For the above reasons, Appellants submit that claims 34 and 37 are definite and respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be reversed.

II. CLAIMS 19-37 ARE ENABLED UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR MAKING AND USING COMPOUNDS WITHIN THE SCOPE OF THESE CLAIMS.

Claims 19-37 stand rejected under 35 U.S.C. § 112, first paragraph, for lacking sufficient enablement for the making and using compounds within the scope of these claims. The Final Office Action contends that the specification does not enable the scope of the claimed (1) R^3 and R′ heterocyclic moieties and (2) N-heterocyclic moieties formed by R^4 and R^5, together with the nitrogen atom to which they are bonded. Appellants respectfully appeal the final rejection of these claims.

It is well established that Appellants are entitled to a presumption of enablement. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Specifically,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. (emphasis added).
>
> *In re Marzocchi and Horton*, 169 USPQ 367, 370 (C.C.P.A. 1971).

The Final Office Action fails to provide a single technical reason or a hint of objective evidence to rebut the presumption of enablement relating to use of the claimed invention. Instead, the Final Office Action states "only one compound falling within the elected restriction group were [*sic*] only tested for enzyme inhibition, antiviral activity, and cell toxicity, where the R^3 is methyl, and the R^4 and R^5 come together to form

saturated isoquinoline." This one observation is offered as allegedly bearing on the 5th, 6th, and 7th of the so-called *Wands* factors.

The compound within falling within the scope of claim 19 that is exemplified, tested, and proven to be a potent retroviral protease inhibitor in Table 1 on page 160 (1st entry) contains a saturated isoquinoline R^4/R^5 structure, which is a nitrogen-containing heterocyclic ring. In any event, the number of compounds tested has absolutely no bearing on the 5th *Wands* factor, which is the level of predictability *in the art.* Furthermore, the Final Office Action's contention that "[t]he applicant does not test the whole breadth of compounds encompassing all of the moieties that these particular radicals can be" is misguided. It is manifest that no working examples are required to satisfy enablement, let alone examples directed to every claimed radical group. *In re Fouche*, 169 USPQ 429, 434 (C.C.P.A. 1971). Nevertheless, the high chemical and biological activity and low toxicity of the compounds tested according to the enzyme and CEM cell assays are as described and reported at 154, line 14 to page 161, line 3.

The Final Office Action provides no objective evidence showing that even a single claimed compound would not possess inhibitory activity. Instead, the Final Office Action states summarily that the *Wands* factor on undue experimentation is satisfied merely because multiple radical groups are claimed.

During the July 3, 2003, personal interview, the Examiner suggested a lack of enablement could be found because potency may be affected when these radicals are interchanged. However, the key to a rejection based on lack of enablement is whether *undue* experimentation is required. In the claimed invention, the compounds inhibit retroviral protease. Undue experimentation is not required to identify an inhibitory

compound. Because the compounds necessarily do not have identical potency (*Fouche*, 169 U.S.P.Q. at 434), it likely will be necessary to adjust dosage. However, such dosage adjustments are *not* considered *undue* experimentation. *US v. Telectronics*, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Rather, dose/response studies are within the skill of a practitioner, and do not constitute undue experimentation. *Telectronics*, 8 U.S.P.Q. 2d at 1224.

The Final Office Action fails to rebut the presumption of enablement of a skilled practitioner's ability to make the claimed invention. The Final Office Action provides neither rationale why nor evidence that a person skilled in the art would have doubted that any of the claimed compounds could have been routinely made according to procedures detailed in the specification, or that any such compound would possesses the asserted utility as a retroviral protease inhibitor. Indeed, numerous methods of making the compounds are described at page 25, line 4, to page 154, line 12, of the specification. Methods of using the invention are described at page 161, line 8, to page 168, line 9.

Nothing in the record suggests that undue experimentation would have been required to (i) synthesize compounds within the claims, and (ii) test the compounds for protease inhibition activity as described in the specification with a reasonable expectation that the tested compound would exhibit some degree of the asserted activity.

In summary, Appellants respectfully submit that the Examiner's subjective feeling about the number of examples is not a well-founded legal position. Rather, the Final Office Action improperly tries to shift the burden to Appellants to demonstrate that the claims are enabled, without first providing the legally required, objective evidence to question the asserted enablement of the claimed compounds. The rejection therefore

completely ignores the presumption of enablement to which Appellants are entitled. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

For the above reasons, Appellants respectfully submit that claims 19-37 are enabled and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reversed.

Additional Considerations Supporting the Definiteness and Enablement of Claims 19-37

In further support of Appellants' above remarks regarding definiteness (Issue I) and enablement (Issue II), Appellants note that many issued U.S. patents having specifications comparable in scope to Appellants' specification are routinely found to support the issuance of claims comparable in scope to Appellants' claims. All issued U.S. patents are presumed valid and their claims are thus presumed to satisfy all patentability requirements, including those of 35 U.S.C. § 112. 35 U.S.C. § 282.

One issued U.S. patent of particular relevance to the questions of definiteness and enablement in the present application is U.S. Patent No. 6,538,006. This patent is related to U.S. Provisional Application No. 60/092,090, as is the present application. Indeed, it is believed that the specification of the '006 patent is identical to the specification of the present application.

The claims of the '006 patent, directed to compounds of Formula III as disclosed in the present application, also recite Markush-type definitions of the pendant moieties R^1, R^2, R^3, R^4/R^5, R^6, and Y'. These definitions are identical to those recited in claims 19-37 of the present application. Furthermore, issued claims 16 and 22 are directed to a method of inhibiting a retroviral infection (corresponding to claim 34 herein) and a method of treating AIDS comprising administering a pharmaceutical composition of the

invention together with other drugs for the treatment of AIDS or the symptoms of AIDS (corresponding to claim 37 herein). Appellants respectfully submit that this issued U.S. Patent No. 6,538,006 is evidence that claims 34 and 37 are definite and that claims 19-37 are enabled.

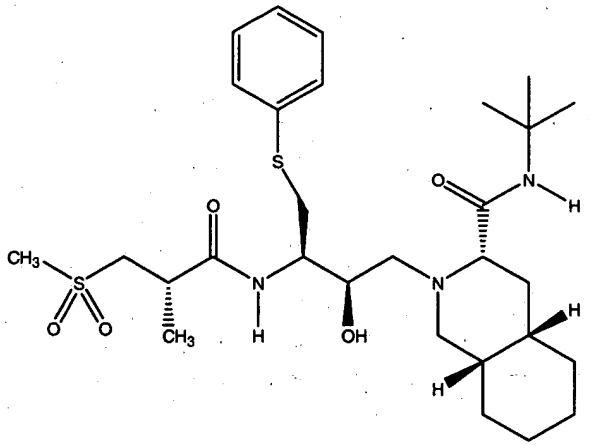
III. AFTER APPELLANTS COMPLIED WITH THE ELECTION OF SPECIES REQUIREMENT, NONE OF THE THREE *ADDITIONAL* PROPOSED RESTRICTION REQUIREMENTS SET FORTH A RESTRICTION GROUP THAT ENCOMPASSES APPELLANTS' ELECTED SPECIES.

To date, one original restriction requirement and three additional restriction requirements were imposed on Appellants' originally filed claims 1-99. In response to the original restriction requirement, Appellants elected a species and identified the subgroup of claims 19-37 as reading thereon. Subsequently, three additional restriction requirements have been entered, each of which purports to be based on a "liberal interpretation of the doctrine of legal and chemical equivalence". For detailed reasons given below, Appellants respectfully submit that these three additional restriction requirements not only fail to set forth a restriction group encompassing Appellants' elected species (Issue III), but also are procedurally and substantively improper (Issue IV).

A. The Original Restriction Requirement (June 5, 2001)

The Office Action dated June 5, 2001, imposed a Restriction Requirement on originally-filed claims 1-99. Appellants were required under 35 U.S.C. § 121 to elect a single disclosed species. In response, Appellants elected the species of Example 22, set forth at page 147, lines 16-23.

The elected species has the structure



and is within the scope of Formula II of claim 19, wherein R′ is methyl (alkyl), t is 0, R^{20} is H (hydrogen), R^{21} is H (hydrogen), R^1 is methyl (alkyl), Y′ is O (oxygen), R^6 is H (hydrogen), R^2 is phenylthiomethyl (arylthioalkyl), and R^4 and R^5 together with the nitrogen to which they are bonded represent an N-heterocycle[1]. Appellants also identified claims 19-37 as reading on this compound and its use.

B. The First *Additional* Restriction Requirement (December 4, 2001)

The following Office Action, dated December 4, 2001, noted the election of the above species and further stated, "The Examiner will now use this species as a reference point to create a natural genus based on a liberal interpretation of the doctrine of legal and chemical equivalence and restriction will be required under 35 U.S.C. § 121." The Examiner identified allegedly separate inventions, directed to compounds of Formula I, as follows:

I. Claims 19-37, drawn to the compound of formula I where R1 is all moieties not containing a heterocyclic ring, t is 2, R2 is arylthioalkyl, a method of

[1] Specifically, the N-heterocycle corresponds to the structure D on page 22 of the specification, wherein q is 1 and R^9 is t-butylcarbamoyl (a monoalkylcarbamoyl, described on page 23, lines 5-8).

treating classified in class 546, subclass 146 and class 514 sublcass 307.

II. Claims 1-99, drawn to the compounds of formula I where R1, R20, and R21, R21, and R2 are all other moieties not covered in group I, and a method of treating classified in various classes, subclasses.

In response to this further restriction requirement, Appellants respectfully submitted that it was impossible to select a group for prosecution because the substituents t, R^{20}, and R^{21} do not appear in Formula I. Furthermore, the elected species is not a compound of Formula I. Appellants also pointed out that, even if the identification of Formula I was a typographical error and the restriction was intended to be based on Formula II, the groups would still make no sense because t cannot be 2 in Formula II. Because the proposed restriction groups are not found in the application, Appellants could not select a group satisfying the restriction requirement. Nevertheless, to at least satisfy the practice requirement that a group be selected in response to a restriction, Appellants selected that group (whatever it might be) in which the Examiner intended the species of Example 22 to fall.

C. The Second *Additional* Restriction Requirement (July 16, 2002), Made Final

In response to Appellants comments, the following Office Action, dated July 16, 2002, modified the restriction as follows:

> Genus I, drawn to claims 19-37, concerns a compound of Formula II in claim 19 where t is 0 to 1, R1=R20=R21 are all moieties claimed except the amino acid side chains claimed, R2 is as claimed, R'=R3 is all moieties claimed except heterocycloalkly, heteroaryl, heterocycloalkylalkyl, and heteroaralkyl radicals, R6 is H, alkyl, R4 and R5 come together with the nitrogen to which they are attached to form a hydrogenated isoquinolinyl which would include rings D, E, and F when Q is 1.
>
> The elected species of example 22 now reads on the elected invention.

In their response to this second additional restriction requirement, Appellants again submitted that the elected species is not a member of the genus to which the Examiner sought to limit prosecution. In particular, the elected species requires, *inter alia*, that R′ be methyl and R^{20} and R^{21} be H. Thus, the elected species cannot be a member of a genus in which "$R' = R^{20} = R^{21}$".

Without addressing these arguments, the Office Action dated January 14, 2003 rendered the restriction requirement **final**. The Examiner asserted that

> The elected species does fit into the natural genus of group I because R3 of formula II can equal alkyl, t can equal 1, R1 can equal alkyl, R20 and R21 can equal alkyl, Y1 can equal oxygen, R6 can equal H, R2 can equal alkylthioaryl, and R4 and R5 can form a nitrogen heterocyclic ring.

However, Appellants could not understand the significance of this statement because, as explained above, in the elected species, R^3 is **not** alkyl[2], t is **not** 1, and R^{20} and R^{21} are **not** alkyl, and R^2 is **not** alkylthioaryl[3]. Appellants therefore sought to understand the nature of the first and second additional restriction requirements in a personal interview.

D. Finality of the Second *Additional* Restriction Requirement Withdrawn

In the personal interview between the Examiner and Appellants' undersigned representatives on July 3, 2003, Appellants again submitted that the requirement to

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[2] R^3 is in fact nonexistent in the elected species, because Y′ is O (oxygen) and not a radical of the formula NR^3. In an Examiner interview on July 3, 2003, Appellants' representatives suggested that the Examiner might have meant that R′ can be methyl, since R′ represents radicals as defined for R^3 and R^3 can be methyl. Appellants requested clarification in the record on this point (*i.e.*, how R′ of the elected species fits the restriction group) in the written interview summary, but none was made.

[3] In the elected species, R^2 is phenylthiomethyl, which is an arylthioalkyl group, signifying attachment of the alkyl (not aryl) part of this group to the core molecule. Appellants pointed out this nomenclature issue in the July 3, 2003 Examiner interview, requesting clarification in the record on this point (*i.e.*, how R^2 of the elected species fits the restriction group) in the written interview summary, but none was made.

restrict claims 19-37 to compounds of the "natural genus" wherein "R^1=R^{20}=R^{21}" was inconsistent with the elected species. Appellants' representatives also pointed out that the Examiner's assertions regarding the possibilities for R^3, t, R^{20}, R^{21}, and R^2 in the Final Office Action were, for reasons given above, not a basis for asserting that the elected species falls into the "natural genus" of Group I.

In the interview, the Examiner agreed that t is 0, not 1, in the elected species. The Examiner also agreed that R^3, although recited in the restriction requirement, does not appear in the structural Formula II set forth in claim 19. The Examiner further agreed that it was appropriate to withdraw the finality of the outstanding Office Action. Appellants' representatives requested clarification insofar as the Examiner mischaracterized the elected species and its relationship to the Formula II.

E. Withdrawn Restriction Requirement Lasted Only One Business Day; Third *Additional* Restriction Requirement Entered

In subsequent telephone conferences on July 8, 2003 with Appellants' representatives, the Examiner stated that the finality of the Office Action would not be withdrawn, because, even though the restriction requirement entered at Paper No. 9 was confusing and poorly phrased, it encompassed the elected species (the compound of Example 22). Appellants again disagreed that the requirement "R^1=R^{20}=R^{21}" encompassed the elected species, at least because R^1 does not equal R^{20} or R^{21}. Thereafter, the Examiner issued an Interview Summary of both the July 3, 2003 and July 8, 2003, personal and telephonic interviews, respectively, asserting the propriety of the second *additional* restriction requirement (July 16, 2002). In this interview summary, the

Examiner "clarified" what was actually meant by the original restriction requirement, which had already been made final well before this point. However, this "clarification" is in fact merely the imposition of yet another restriction requirement, namely, a third *additional* restriction requirement.

Based on the above, Appellants submit that the proposed Group I of the restriction requirement imposed on December 14, 2001, and modified on July 16, 2002, was not drawn to subject matter reading on the elected species. Therefore, rendering this restriction requirement final in the January 14, 2003, Office Action was improper.

Reversal of the restriction requirement on this ground is therefore respectfully requested.

IV. AFTER ELECTION OF SPECIES, APPELLANTS ARE ENTITLED TO EXAMINATION ON THE MERITS OF THE ENTIRE CLAIMS 19-37, WHICH READ ON THAT SPECIES.

Appellants submit that the Restriction Requirement imposed in the December 4, 2001, Office Action, is in direct contrast to well-established examination principles set forth MPEP § 803.02, relating to restriction practice for Markush claims. Importantly, this restriction requirement is a further requirement. In the June 5, 2001, Office Action, Appellants first elected a species (*i.e.*, the compound of Example 22 on page 147, lines 16-23 of the specification) for examination, and identified claims 19-37 as reading thereon[4]. The Examiner then made this further restriction requirement based on "a liberal interpretation of the doctrine of legal and chemical equivalence."

[4] Importantly, after the election of species, claims 19-37 were rejected under 35 U.S.C § 102(b) and this rejection was overcome. Accordingly, claims 19-37 are allowable on the merits, save for the 35 U.S.C § 112 rejections now on appeal.

Appellants respectfully submit the further restriction requirement is directly contrary to MPEP § 803.02. In particular, after Appellants complied with the election-of-species requirement, they were entitled to full examination on the merits of claims 19-37, reading on the elected species. According to the above-cited MPEP section, in Markush claim practice,

> ...the examiner may require a provisional election of a single species prior to examination on the merits. ...Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration. (emphasis added).
>
> . . . .
>
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a *non-elected species*, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration.

Furthermore, the MPEP requires full examination of claims 19-37, reading on the elected species, regardless of whether these claims encompass independent inventions. Specifically, MPEP § 803.02 provides

> If the members of the Markush group are ...so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. (emphasis added).

The fact that the proposed restriction would have split the claims into only two groups *(i.e.*, the "natural genus" and everything else) negates any of the Examiner's contentions as to the burden of examining the claims 19-37 in their entirety.

Furthermore, MPEP § 803.02 states, "[I]t is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention." (emphasis added). Unity of invention is based on well-settled judicial precedent[5]. For example, the MPEP cites *In re Harnisch* and *Ex parte Hozumi*. 206 U.S.P.Q. 300 (C.C.P.A. 1980) and 3 U.S.P.Q.2d 1059 (Bd. Pat. App. & Int. 1984). In *Harnisch*, the Court of Customs and Patent Appeals rejected the imposition of a restriction requirement in a Markush-type claim where all of the compounds had a single use, and thus had unity of invention. Likewise, in *Hozumi*, the Board of Patent Appeals and Interferences (hereinafter "Board") reversed a rejection of a Markush-type claim, where the compounds were core structures having plural diverse pendant moieties.

Other decisions reinforce the proposition that unity of invention is based on a common utility. For example, in *In re Jones*, the Court of Customs and Patent Appeals reversed the Board's 'improper Markush group' rejection precisely because the claimed compounds had a common function. 162 F.2d 479, 74 U.S.P.Q. 149 (C.C.P.A.1947). In *Ex parte Dahlen*, 42 U.S.P.Q. 208 (Bd. App. 1938), the Board permitted claims to compounds having a common core with pendant widely-varying side chains, because the claimed compounds had a community of properties.

Based on the above decisions, claims 19-37 have unity of invention, because these claims embrace a single inventive concept. The compounds of claim 19 are retroviral protease inhibitors. These have a single common core and pendant moieties, as set forth in the definitions of R', t, R^{20}, R^{21}, R^1, Y', R^6, R^2, R^4, and R^5. No matter which

[5] In the Examiner interview on July 3, 2003, Appellants' representatives clarified to the Examiner that the term "unity of invention" as it applies to U.S. restriction practice is not the same as that used under the PCT articles to restrict inventions.

combination of pendant moieties is selected, the resulting compound is a retroviral protease inhibitor. Such compounds may also have other uses, but all are retroviral protease inhibitors. To restrict claims 19-37 to any scope less than their full scope is contrary to established precedent and MPEP guidance.

In summary, Appellants elected a species, in response the restriction requirement imposed in the Office Action dated June 5, 2001. Established procedures of MPEP § 803.02 require full examination of claims reading on the elected species. For these reasons, Appellants respectfully submit that the Examiner's requirement to further restrict these claims to specified Markush members is improper.

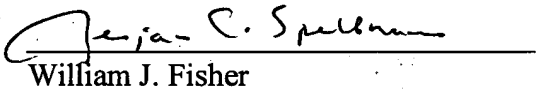
Reversal of the restriction requirement on this ground is therefore respectfully requested.

SUMMARY

In view of the arguments presented herein, claims 19-37 are patentable. Reversal of the rejections under 35 U.S.C. § 112, 1st and 2nd paragraphs, as well as reversal of the further restriction requirement of claims 19-37 to specified Markush members, is respectfully requested.

Respectfully submitted,

Date: November 13, 2003

By: 

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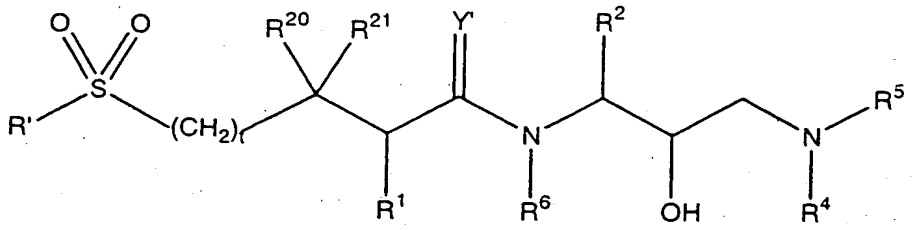
APPENDIX I
Appealed Claims 19-37

19. A compound represented by the formula:



(Formula II)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

R' represents radicals defined for R^3;

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-CH_2C(O)NHCH_3$, $-CH_2C(O)N(CH_3)_2$, alkyl, alkylthioalkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl, alkoxyalkyl, haloalkyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine,

glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents O, S and NR^3;

R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocycle;

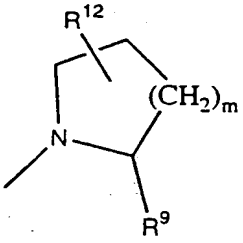
R^6 represents hydrogen and alkyl radicals;

and R^{20} and R^{21} represent radicals as defined for R^1.

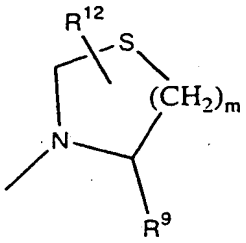
20. A compound of Claim 19 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged monocyclic, 11, 12 or 13 members when bicyclic, and 11

to 16 members when tricyclic; and R^6 represents hydrogen and alkyl radicals. —

21. A compound of Claim 20 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



(A)



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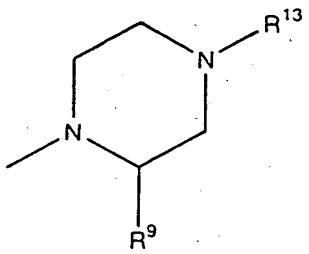

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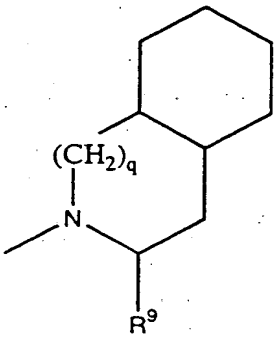

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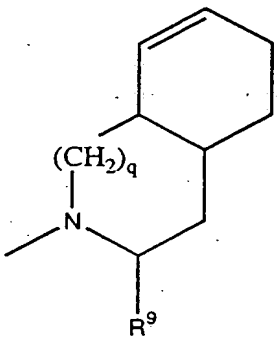

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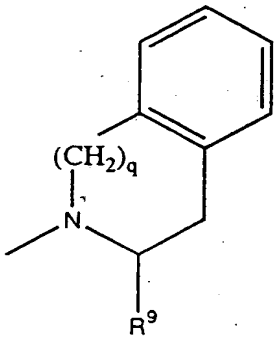

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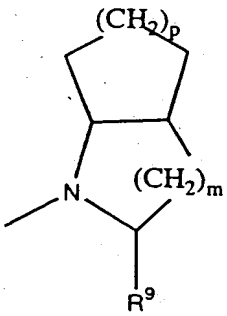
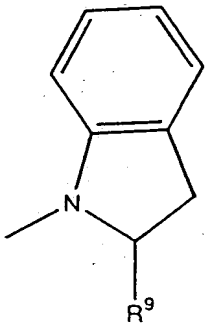
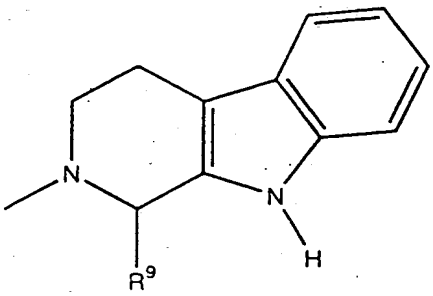


(G)



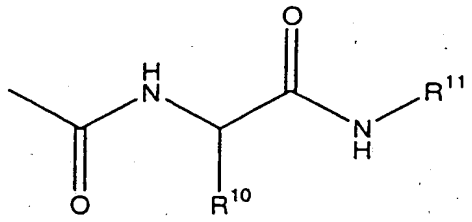
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^6 represents hydrogen and alkyl radicals.

22. A compound of Claim 19 where Y' is oxygen.

23. A compound of Claim 19 where R^2 is arylthioalkyl.

24. A compound of Claim 19 where t is 0.

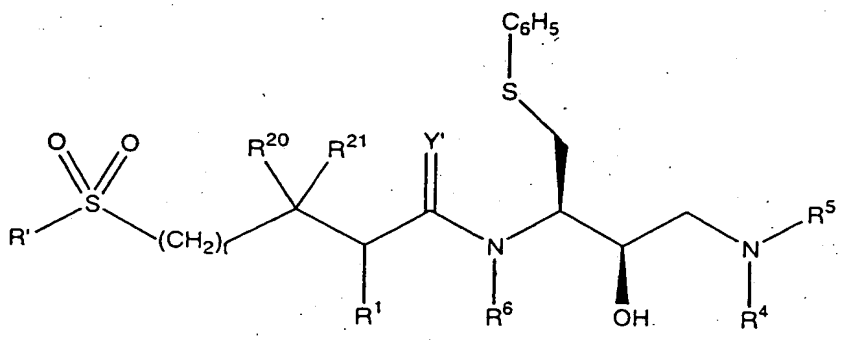
25. A compound of Claim 20 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

26. A compound of Claim 19 where R^{20} and R^{21} are hydrogen or alkyl.

27. A compound of Claim 19 where R'is alkyl, aryl or arylalkyl.

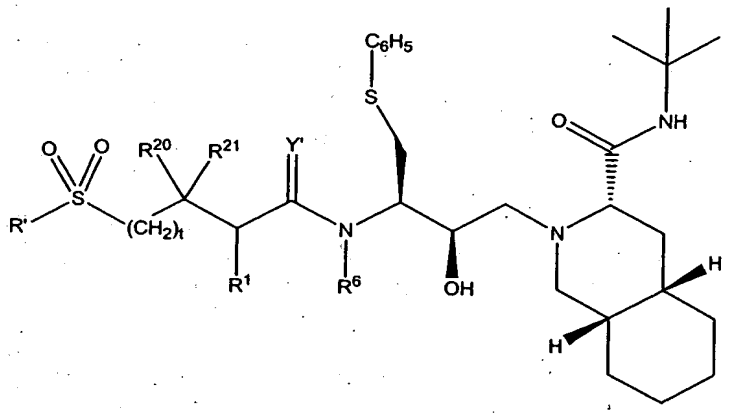
28. A compound of Claim 19 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

29. A compound of Claim 19 represented by the Formula



wherein R', R^1, R^6, R^4, R^5, R^{20}, R^{21}, Y' and t are as described herein.

30. A compound of Claim 21 represented by the formula



wherein R′, R^1, R^6, R^4, R^5, R^{20}, R^{21}, t, and Y′ are as described herein.

31. A pharmaceutical composition comprising a compound of Claim 19 and a pharmaceutical carrier.

32. A pharmaceutical composition comprising a compound of Claim 19 and pharmaceutical carriers.

33. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 19.

34. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 19.

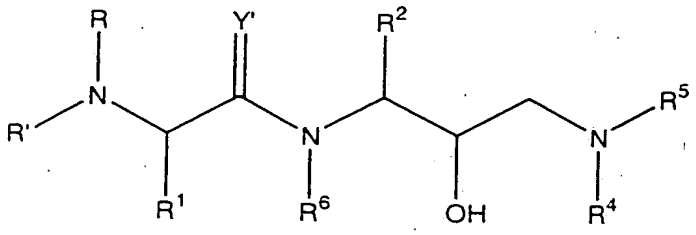
35. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 19.

36. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 19.

37. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 19 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

APPENDIX II
Pending and Withdrawn Claims 1-18 and 38-99

1. A compound represented by the formula:



(Formula I)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

R represents hydrogen, alkoxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbanoyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocycloxycarbonyl, heteroaralkoxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroarylcarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aralkylaminoalkylcarbonyl, aminoalkanoyl, aminocarbonyl, aminocarbonylalkyl, alkylaminoalkylcarbonyl, and mono- and disubstituted

aminocarbonyl and aminoalkanoyl radicals wherein the substituents are selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, alkoxycarbonyl, arylalkyloxycarbonyl, and heterocycloalkylalkyl radicals, or in the case of disubstituted aminoalkanoyl, said substituents along with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl radical;

R' represents radicals defined for R^3, or R and R' together with the nitrogen to which they are attached form a heterocycloalkyl or heteroaryl radical;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(0)NH_2$, $-C(0)NHCH_3$, $-C(0)N(CH_3)_2$, $-CH_2C(0)NHCH_3$, $-CH_2C(0)N(CH_3)_2$, alkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, haloalkyl, alkoxyalkyl, alkynyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine, side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group

consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

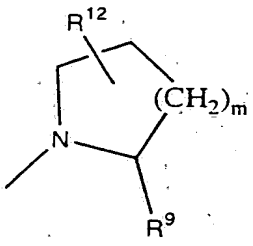
R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents O, S and NR^3;

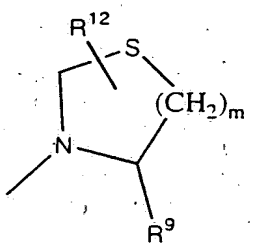
R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety; and R^6 represents hydrogen and alkyl radicals.

2. A compound of Claim 1 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged monocyclic, 11, 12 or 13 members when bicyclic, and 11 to 16 members when tricyclic.

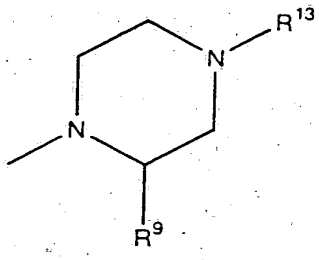
3. A compound of Claim 2 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including
(J)



(A)



(B)



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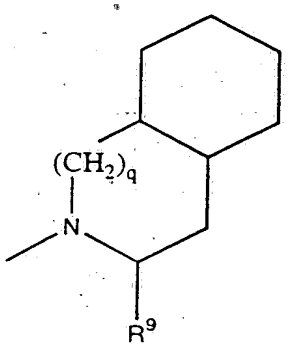
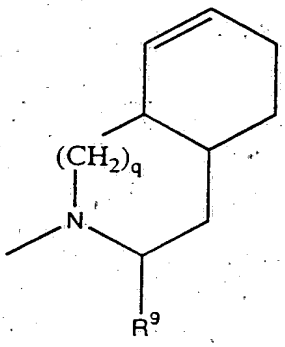
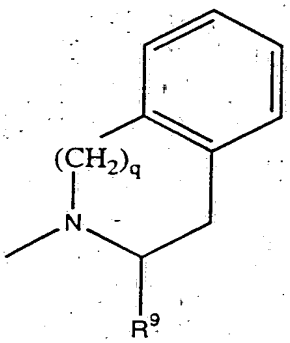


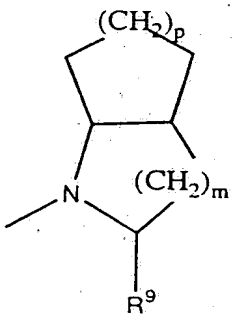
(D)



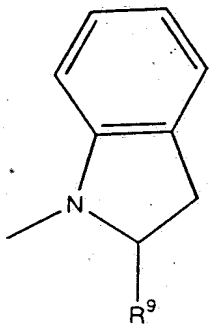
(E)



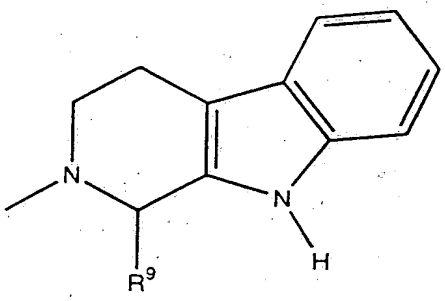
(F)



(G)



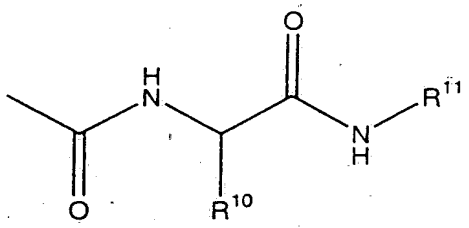
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^6 represents hydrogen and alkyl radicals.

4. A compound of Claim 1 where Y' is oxygen.

5. A compound of Claim 1 where R^2 is arylthioalkyl.

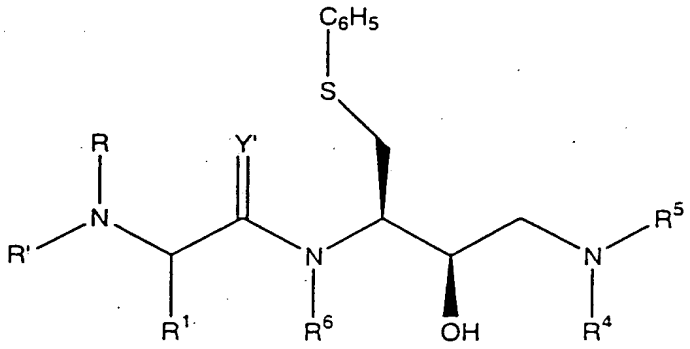
6. A compound of Claim 2 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

7. A compound of Claim 1 where R is hydrogen, alkoxycarbonyl, arylalkylcarbonyl, heterocyclecarbonyl, aminoalkanoyl, mono-substituted aminoalkanoyl, di-substituted aminoalkanoyl.

8. A compound of Claim 1 where R'is hydrogen.

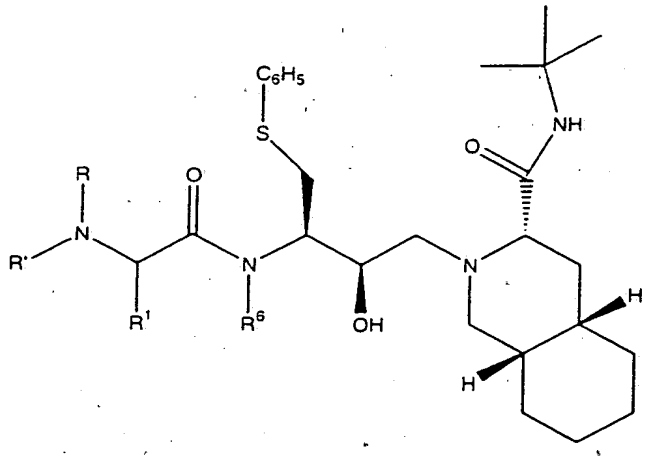
9. A compound of Claim 3 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

10. A compound of Claim 1 represented by the formula



wherein R, R', R^1, R^6, Y', R^4 and R^5 are as described herein.

11. A compound of Claim 3 represented by the formula



wherein R, R', R^1, R^6 and Y' are as described herein.

12. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutical carrier.

13. A pharmaceutical composition comprising a compound of Claim 1 and pharmaceutical carriers.

14. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 1.

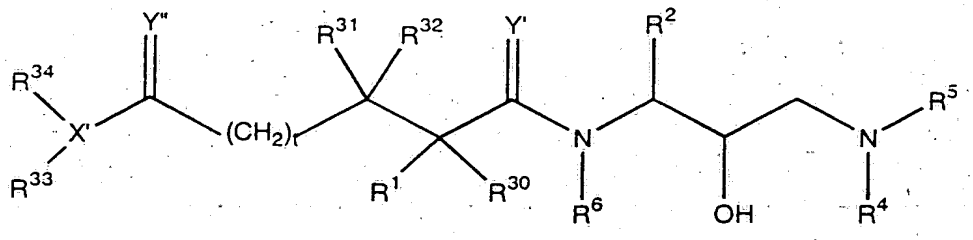
15. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 1.

16. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 1.

17. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 1.

18. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 1 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

38. A compound represented by the formula:



(Formula III)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-CH_2C(O)NHCH_3$, $-CH_2C(O)N(CH_3)_2$, alkyl, thioalkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl, alkoxyalkyl, haloalkyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine,

phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl, or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

X' represent O, N and $C(R^{17})$ where R^{17} represents hydrogen and alkyl radicals;

Y' and Y" independently represent O, S and NR^3;

R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocycle;

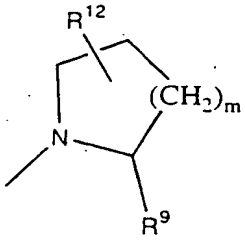
R^6 represents hydrogen and alkyl radicals;

R^{30}, R^{31} and R^{32} independently represent radicals as defined for R^1, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical; and

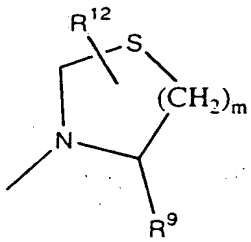
R^{33} and R^{34} independently represent radicals as defined for R^3, or R^{33} and R^{34} together with X' represent cycloalkyl, aryl, heterocyclyl and heteroaryl radicals, provided that when X' is O, R^{34} is absent.

39. A compound of Claim 38 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged monocyclic, 11, 12 or 13 members when bicyclic, and 11 to 16 members when tricyclic; and R^5 represents hydrogen and alkyl radicals.

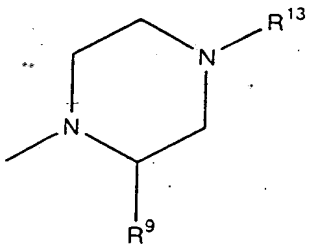
40. A compound of Claim 39 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



(A)



(B)



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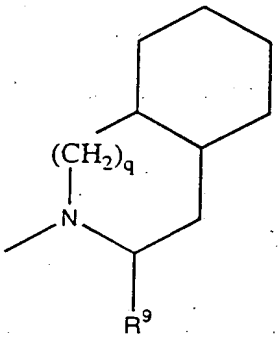

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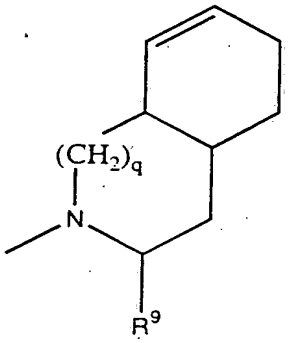
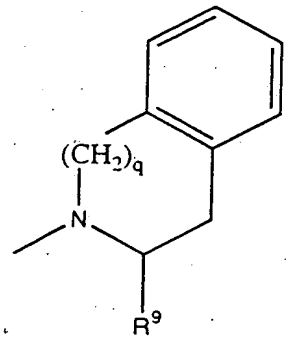
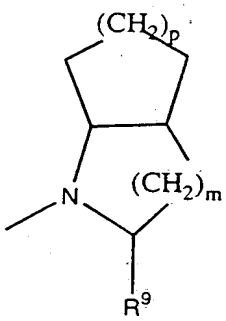


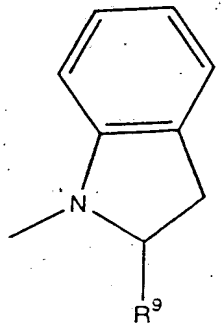
(E)



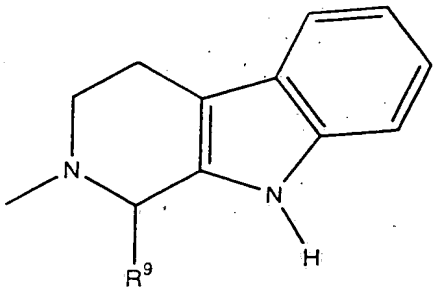
(F)



(G)



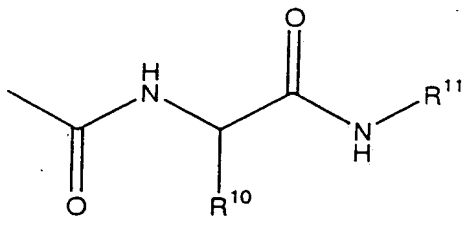
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^5 represents hydrogen and alkyl radicals.

41. A compound of Claim 38 where Y' and Y" are oxygen.

42. A compound of Claim 38 where R^2 is arylthioalkyl.

43. A compound of Claim 38 where t is 0.

44. A compound of Claim 39 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

45. A compound of Claim 38 where X' is oxygen.

46. A compound of Claim 38 where X' is nitrogen.

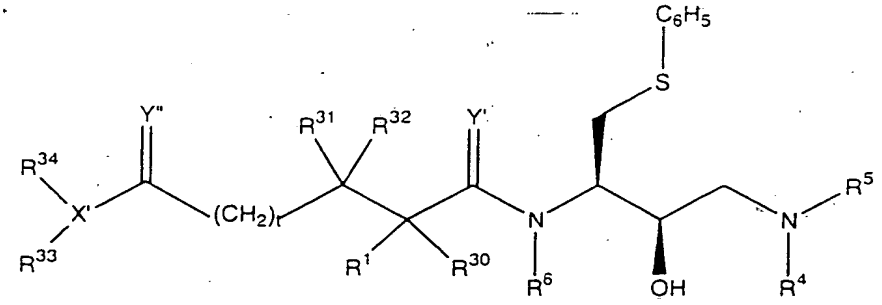
47. A compound of Claim 38 where R^{33} and R^{34} are hydrogen, alkyl, cycloalkyl, aralkyl or haloalkyl.

48. A compound of Claim 38 where R^{33} and R^{34} taken together with the nitrogen to which they are attached form a heterocyclic ring.

49. A compound of Claim 40 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

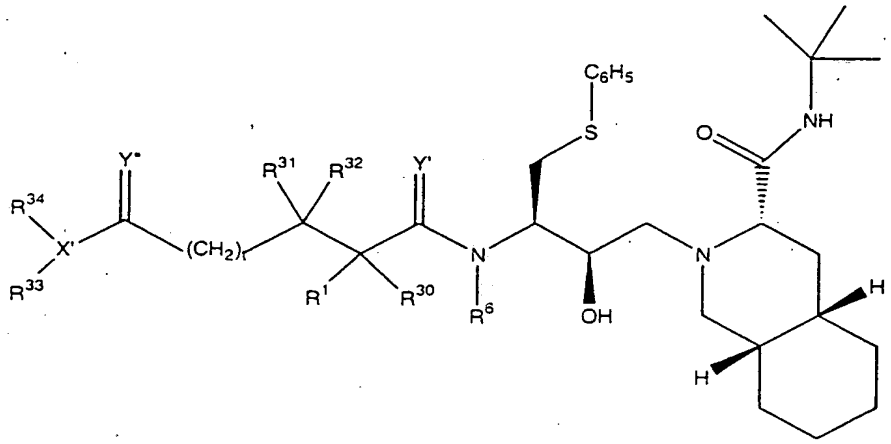
50. A compound of Claim 38 where R^1, R^{30}, R^{31}, R^{32} are hydrogen or alkyl.

51. A compound of Claim 38 represented by the Formula



wherein R^1, R^6, Y'; Y", R^4, R^5, R^{30}, R^{31}, R^{32}, R^{33}, R^{34} and t are as described herein.

52. A compound of Claim 40 represented by the formula



wherein R, R', R^1, R^6 and Y' are as described herein.

53. A pharmaceutical composition comprising a compound of Claim 38 and a pharmaceutical carrier.

54. A pharmaceutical composition comprising a compound of Claim 38 and a pharmaceutical carriers.

55. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 38.

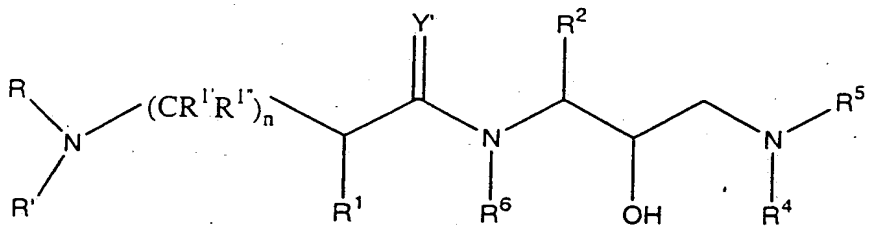
56. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 38.

57. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 38.

58. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 38.

59. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 38 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

60. A compound represented by the formula:



(Formula IV)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

R represents hydrogen, alkoxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbanoyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocycloxycarbonyl, heteroaralkoxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroarylcarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aralkylaminoalkylcarbonyl, aminoalkanoyl,

aminocarbonyl, aminocarbonylalkyl, alkylaminoalkylcarbonyl, and mono- and disubstituted aminocarbonyl and aminoalkanoyl radicals wherein the substituents are selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of disubstituted aminoalkanoyl, said substituents along with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl radical;

R' represents radicals defined for R^3, or R and R' together with the nitrogen to which they are attached form a heterocycloalkyl or heteroaryl radical;

n represents 1 or 2;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(0)NH_2$, $-C(0)NHCH_3$, $-C(0)N(CH_3)_2$, $-CH_2C(0)NHCH_3$, $-CH_2C(0)N(CH_3)_2$, alkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl, haloalkyl, alkoxyalkyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^3;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl, or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents O, S and NR^3;

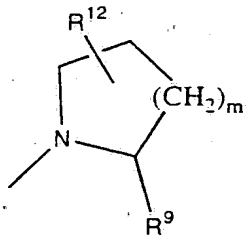
R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocylic moiety;

R^6 represents hydrogen and alkyl radicals.

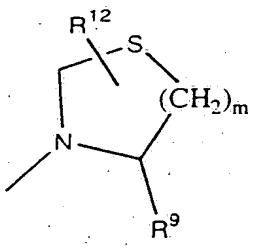
61. A compound of Claim 60 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged monocyclic, 11, 12 or 13 members when bicyclic, and 11 to 16 members when tricyclic.

62. A compound of Claim 60 where n is 1.

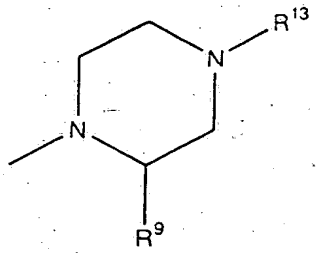
63. A compound of Claim 60 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



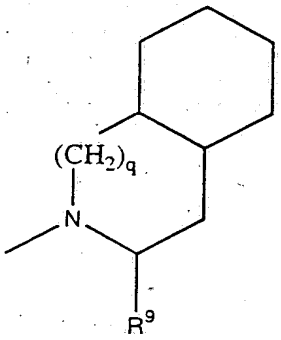
(A)



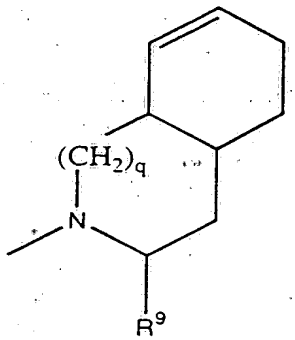
(B)



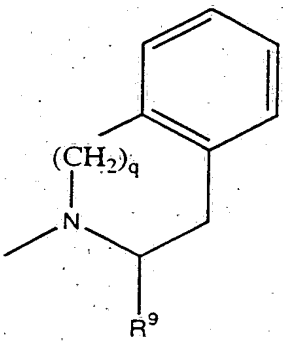
(C)



(D)



(E)



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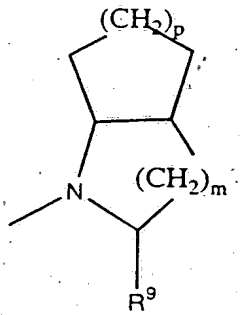
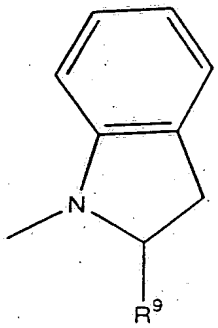
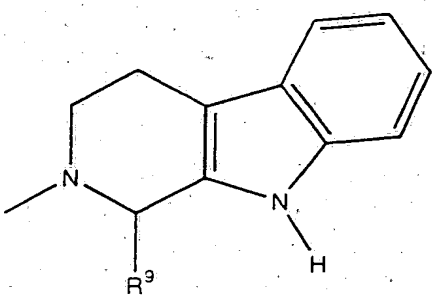


(G)



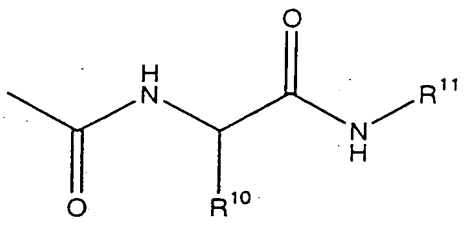
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^5 represents hydrogen and alkyl radicals.

64. A compound of Claim 60 where Y' is oxygen.

65. A compound of Claim 60 where R^2 is arylthioalkyl.

66. A compound of Claim 61 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

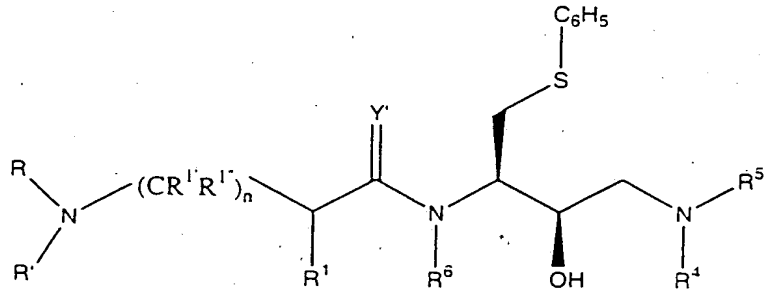
67. A compound of Claim 60 where R is hydrogen, alkoxycarbonyl, arylalkylcarbonyl, heterocyclecarbonyl, aminoalkanoyl, mono-substituted aminoalkanoyl, di-substituted aminoalkanoyl.

68. A compound of Claim 62 where $R^{1'}$ and $R^{1''}$ are hydrogen.

69. A compound of Claim 60 where R' is hydrogen.

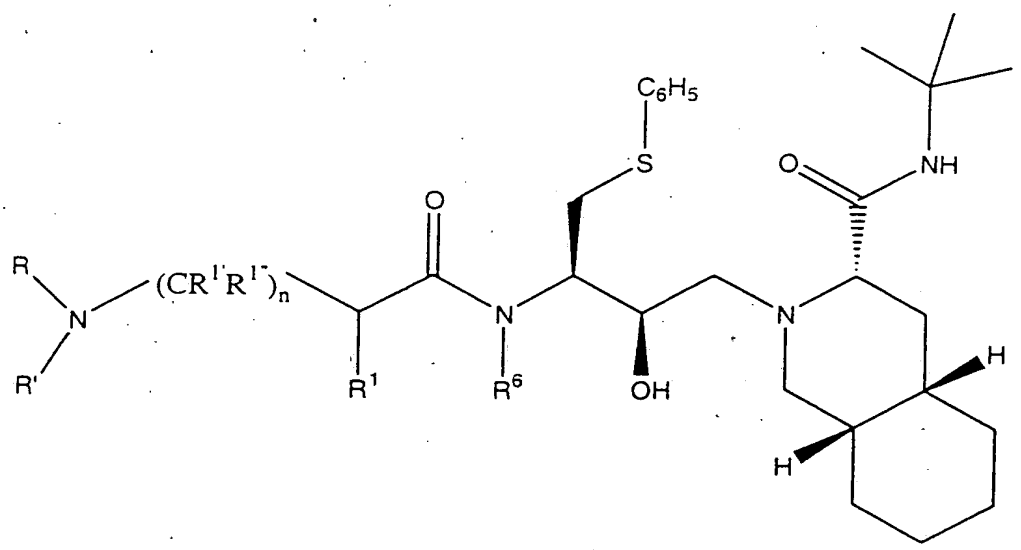
70. A compound of Claim 60 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

71. A compound of Claim 60 represented by the formula



wherein R, R', R^1, $R^{1'}$, $R^{1''}$, R^6, R^4, R^5 and Y' are as described herein.

72. A compound of Claim 63 represented by the formula



wherein R, R', R^1, $R^{1'}$, $R^{1''}$, R^6 and Y' are as described herein.

73. A pharmaceutical composition comprising a compound of Claim 60 and a pharmaceutical carrier.

74. A pharmaceutical composition comprising a compound of Claim 60 and pharmaceutical carriers.

75. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 60.

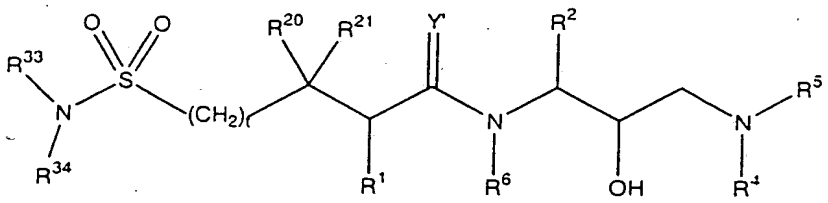
76. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 60.

77. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 60.

78. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 60.

79. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 60 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

80. A compound represented by the formula:



(Formula IIa)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(0)NH_2$, $-C(0)NHCH_3$, $-C(0)N(CH_3)_2$, $-CH_2C(0)NHCH_3$, $-CH_2C(0)N(CH_3)_2$, alkyl, alkylthioalkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents 0, S and NR^3;

R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocycle;

R^6 represents hydrogen and alkyl radicals;

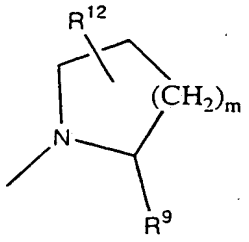
R^{33} and R^{34} independently represent radicals as defined for R^3, or R^{33} and R^{34} together with the nitrogen to which they are attached form heterocyclyl and heteroaryl radicals;

and R^{20} and R^{21} represent radicals as defined for R^1.

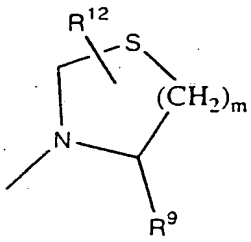
81. A compound of Claim 80 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged

monocyclic, 11, 12 or 13 members when bicyclic, and 11 to 16 members when tricyclic; and R^5 represents hydrogen and alkyl radicals.

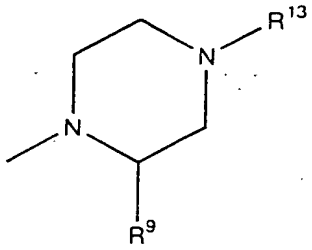
82. A compound of Claim 80 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



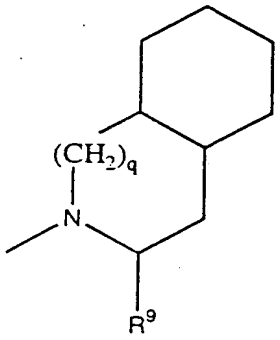
(A)



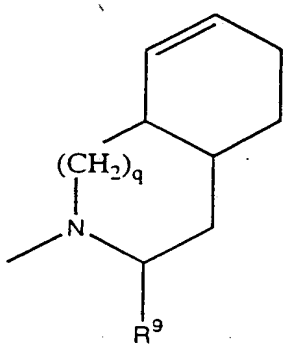
(B)



(C)



(D)



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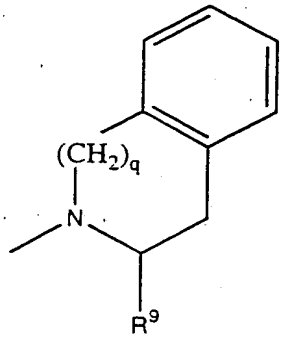
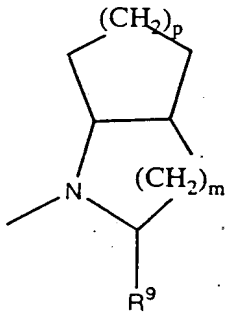
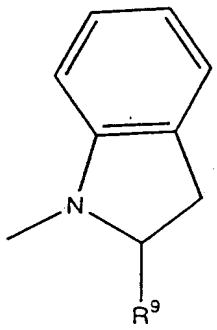


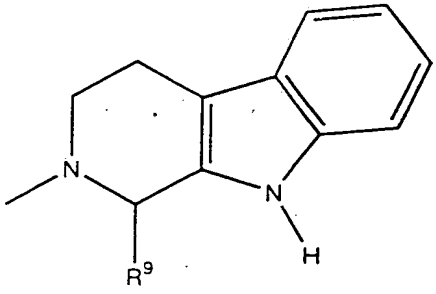
(F)



(G)



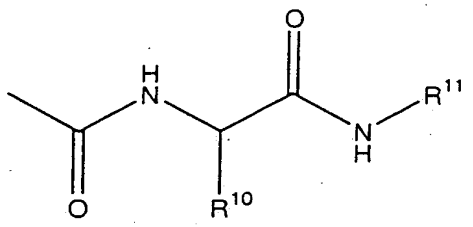
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^5 represents hydrogen and alkyl radicals.

83. A compound of Claim 80 where Y' is oxygen.

84. A compound of Claim 80 where R^2 is arylthioalkyl.

85. A compound of Claim 80 where t is O.

86. A compound of Claim 81 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

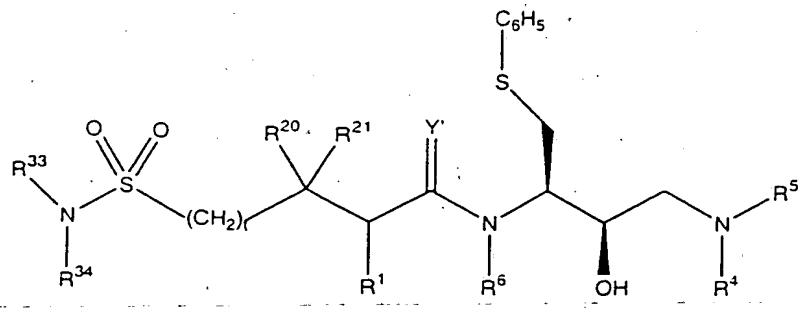
87. A compound of Claim 80 where R^{33} and R^{34} are hydrogen, alkyl, cycloalkyl, aralkyl or haloalkyl.

88. A compound of Claim 80 where R^{33} and R^{34} taken together with the nitrogen to which they are attached form a heterocyclic ring.

89. A compound of Claim 80 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

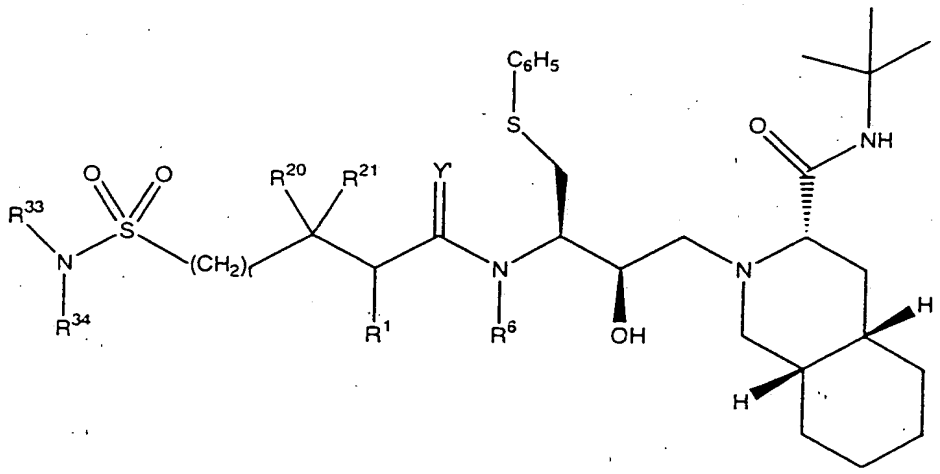
90. A compound of Claim 80 where R^{20} and R^{21} are hydrogen or alkyl.

91. A compound of Claim 80 represented by the Formula



wherein R^1, R^6, R^4, R^5, R^{20}, R^{21}, R^{33}, R^{34}, t and Y' are as described herein.

92. A compound of Claim 82 represented by the formula



wherein R^1, R^6, R^{20}, R^{21}, R^{33}, R^{34}, t and Y' are as described herein.

93. A pharmaceutical composition comprising a compound of Claim 80 and a pharmaceutical carrier.

94. A pharmaceutical composition comprising a compound of Claim 80 and a pharmaceutical carriers.

95. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 80.

96. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 80.

97. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 80.

98. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 80.

99. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 80 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.